CANWELL FILE 9-24-85

7601 / Linuron

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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SEP 24 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of Data Call In Notice for Linuron, Draft of 9/5/85

TO: Ingrid Sunzenauer, Review Manager
Special Review Branch (TS-767C)

and

Robert Taylor, PM #25
Registration Division (TS-767C)

FROM: James N. Rowe, Ph.D.
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Hazard Evaluation Division/HED (TS-769C)

James N. Rowe 9/23/85

THRU: Laurence D. Chitlik, D.A.B.T.
Section Head, Section V
Toxicology Branch/HED (TS-769C)

Laurence D. Chitlik for LDC 9/23/85

and

Theodore M. Farber, Ph.D.
Chief, Toxicology Branch/HED (TS-769C)

9/24/85

ACTION:

Review of data call in notice for linuron, EPA I.D. #035506

RECOMMENDATIONS:

It is recommended that the toxicological data for blood effects in the dog and the data on worker exposure levels and physical examination data be required with the following modifications in wording for the DCI:

4. Toxicological Data Needed:

a. The special dietary testing required in the dog by the Guideline document is required to gather more information on sulf- and methemoglobin formation and to establish a no-observable-effect level (NOEL) for blood parameters including red blood cell precursors such as reticulocytes and organs/tissues involved in hematogenesis, i.e., bone marrow, spleen and liver. A feeding study of 90 days duration ("subchronic") is required with blood analysis at periodic intervals

and histopathology at the end of the dosing period. A protocol must be submitted for Agency review.

b. Data on worker exposure levels to technical linuron, formulations, and relevant precursors and physical examination data (especially information regarding methemoglobinemia and chloracne) are required.

II-B Schedules for Submission of Data

4. Toxicology Studies

- A progress report is due 3 months after receipt of this Notice and semiannually thereafter.

- A final report is due 12 months after receipt of this Notice.

RATIONALE FOR REQUIRED TESTING:

"Subchronic" Testing in the Dog

The acceptable daily intake (ADI) for linuron has been based on a NOEL of 25 ppm from a chronic dog study and a safety factor of 100. Decreased RBC counts and a high incidence of abnormal blood pigments were observed at 125 ppm (Hodge, H.C. et al., 1963, EPA Accession #090386, MRID #00018374. This study was reviewed in the Toxicology Branch chapter of the Linuron Registration Standard by Dr. L. B. Dale). It was the basis of a recent risk assessment for dietary exposure of infants to linuron (C. Aldous, memo of 5/14/85). It was noted by Dr. Aldous that 2 out of 5 dogs fed ppm linuron (the LDT) had an uncharacterized "abnormal pigment" in the blood, as did 4 out of 5 dogs at the 125 ppm level, and all dogs at the 625 ppm level. Thus, a true NOEL has not been established although the "NOEL" employed in the ADI calculations for linuron was nevertheless given as 25 ppm, consistent with the observation that normally measured hematological parameters, e.g., hematocrit, RBC counts, mean corpuscular hemoglobin, etc., were not found to be affected below 125 ppm.

In addition to the dog study, a rat long term feeding study (Kaplan, A.M. et al., 1980, MRID #00029680; Everett, R.M. et al., 1980, MRID #000269679; reviewed by Dr. Dykstra of Toxicology Branch in memo dated May 16, 1980) found hematological effects down to the LDT (50 ppm). At that dose, males had increased mean corpuscular hemoglobin in the absence of changes in hematological or hemoglobin concentration (per ml blood). This was taken by the investigators as an indication of reticulocytosis. Thus there was no NOEL for hematological effects established in the rat study also. A "special dietary exposure" was to be undertaken by the registrant to fill this data gap, as confirmed in a memo from Richard Holt of du Pont to Robert Taylor (PM-25) dated Sept. 21, 1984. This study has been submitted and is presently under review by the Toxicology Branch.

Worker Exposure and Physical Examination Data

3,3',4,4'-tetrachloroazobenzene (TCAB), 3,3',4,4'-tetrachloroazoxybenzene (TCAOB), and dichloroaniline (DCA) are the major contaminants in linuron.

DCA is one of 20 substituted anilines under consideration by the Interagency Testing Committee (ITC) for further testing. The 3,4-DCA isomer in which we are presently interested has been selected to represent a group of polychloroanilines for further toxicological evaluation. Studies will involve oncogenicity, mutagenicity, teratogenicity, reproductive effects, and chronic effects (with emphasis on blood effects). Acute methemoglobinemia is characteristic of anilines, and DCA has been identified as the causative agent for methemoglobinemia in one industrial exposure incident during the manufacture of propanil (Taylor and Lloyd, 1982, unpublished ms.).

TCAB and TCAOB are isomers of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Chloracne is a disease characterized by acneform skin lesions, which has been associated with industrial exposures to a variety of chemicals including TCDD. Chloracne has been reported in several incidents in which TCAB and/or TCAOB were probable causative agents. Some exposed workers had a continuance of symptoms 8 years following exposure, and some were photosensitive. Family members of four exposed workers also contracted chloracne, even though they had never been near the plant (Poland et al, 1976; Taylor et al., 1977, 1979; Taylor, 1974; Taylor, unpubl. ms., as cited in review by J.S. Bellin, 02/26/85).